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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,351	07/30/2001	Makoto Asashima	31671-173644	1990

26694 7590 02/11/2004

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,351	ASASHIMA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 11/21/03 has been entered. No amendment was made. Claims 25-27 are pending in the application and under current examination.

Specification

The disclosure is objected to because of the following informalities:

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e) & § 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

A. In the 11/21/03 response, applicants first state that the term "stage" is not limited to the embryonic state, but can be applied to any distinguishable stage of embryonic, juvenile, or adult stage (Response, page 3, 3rd paragraph).

In response, it is noted that the question was raised because the specification fails to teach how the developmental stages for a vertebrate is defined for embryo, juvenile, and adult life, and it fails to teach any organ developmental stage of any other vertebrate except the embryonic stage of a xenopus. Previous Office action clearly indicated,

"in light of the teaching of the specification, the stage taught in the specification is the embryonic developmental stages of xenopus, such as those illustrated in figures 1, 2, and 4; and the specification is silent with respect to the stages of neonatal, infant, or adult, therefore, the scope of the claims taught in the specification appears to be limited to transplanting *in vitro* induced organ into the *fetus* of a vertebrate rather than matured vertebrates".

Given the plain meaning of English language, the term "stage" does encompass any stage of the life span, and thus, Applicants may use the term as they desired. However, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). As indicated in pages 6 and 7 of the 8/8/03 Office action, the state of the art has seen little success if any in organ culture *ex vivo*. The claimed invention as intended requires inducing an organ from ectoderm region of the blastula, and maintaining the organ development to any stage of the life, including neonatal and adult. However, the specification fails to

teach the conditions required to induce and maintain an organ as broadly encompassed by the claims, and fails to reduce to practice any organ culture other than a xenopus embryo. In view of extremely undeveloped state of the art (which has been detailed in the previous Office action, and will further discuss in the following paragraphs), the specification fails to provide an enabling disclosure to support the full scope of the claims.

B. With respect to the term "blastula", which technically refers to an early *non-mammalian* embryo, applicants cited Merriam Webster's Collegiate Dictionary (1993) acknowledging that a placenta mammal has a modified form of blastula (i.e. blastocyst), and applicants intend to claim both mammal and non-mammal. (Response, page 4, paragraph 3). In response, in addition to the cited 1993 version of the dictionary, the latest version of the Dictionary defines, "IN ORGANISMS SUCH AS MAMMALS, THE EARLIER MORULA DEVELOPS INTO A SOMEWHAT DIFFERENT FORM OF BLASTULA, THE BLASTOCYST". It appears both the earlier and current version of the Merriam Webster's Collegiate Dictionary acknowledge that the terms blastula and blastocyst represent a correspondent stage of the non-mammalian and mammalian embryonic development, and the two are structurally different. Since the specification has not particularly redefine the term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term, the term should only give its plain meaning, i.e. referring to an embryonic developmental stage of a *non*-mammal vertebrate.

C. Applicants then argue that they have provided ample evidence that myriad gene markers are available for human, rat, and mouse, and that similar technique can be used to obtain such markers for any stage of interest. Applicants reiterated the Declaration of Professor Asashima, a JAMS and two other publications as support evincing the availability of the markers, and possibility of inducing an organ from undifferentiated cells. Further, they argue that observation of organ tissues using traditional anatomical, histological, and other observation techniques does not require knowledge of genomic DNA markers (Response, paragraph bridging pages 3 & 4).

In response, pertaining to genomic markers of vertebrate development, the JAMS publication is based on the experimental data on Xenopus development, the publications in journals of DEVELOPMENT and MOLECULAR AND CELLULAR BIOLOGY teach the same type marker, i.e. SALL1 for human and murine. They are not representative stage-specific genomic markers for the genus encompassing any stage of representative vertebrates. Applicants are reminded again that approximately 45,000 living species constitute the vertebrates and about 400 species constitute the amphibians (the subgenus that includes Xenopus). With respect to urodele (belongs to amphibians as does Xenopus), the inventors acknowledge that "LITTLE IS KNOWN ABOUT THE MOLECULAR BACKGROUND OF URODELE EMBRYOS" (right column, page 115, Ariizumi et al, Zoological Sci 1999;16:115-24). Therefore, as indicated in the previous Office actions, the skilled artisan could not practice the invention without first carrying out undue experimentation to determine the developmental stage-specific genomic DNA markers for representative species of the broadly claimed genus. Moreover, even if the stage-

specific genomic DNA marker combined with the anatomical observation could determine the developmental stages for the representative species of vertebrate genus, there are many other foreseeable or unforeseeable barriers preventing full enablement for practicing the recited steps of the claims, which have been discussed in detail in pages 5 through 9 of 8/8/03 Office action.

Pertaining to the issues under 35 U.S.C. § 112, 1st paragraph, the Declaration states that "the basic rule of body formation is common to all the vertebrates and homologous genes", and "the principal of basic differentiation such as development, cell differentiation, organ differentiation, and so on, is common to all vertebrates, and the same is true of different species". The statement is insufficient to overcome the rejection because here the issue is not about the basic rule or principal, but the feasibility of inducing each and every type of organ in representative vertebrates of mammals and non-mammals *in vitro* from a particular stage of an embryo, and maintain such to any stage of the life span, neonatal, juvenile, and adult, which could mean years of maintaining in a proper culture environment an matured organ induced from the ectoderm region of an embryo, such long term organ culture has not been realized even for organs obtained from a fully developed donor. In the previous Office action, the Office has cited numerous teachings by the skilled artisans illustrating that the intrinsic controls that keep stem cells renewable or direct stem cells along particular differentiation pathways (i.e. induced to develop to a desired organ) remain largely unknown as taught by *Watt et al, Donovan and Gearhart*, that molecular requirement for mitotic spindle assembly are qualitatively distinct in higher mammals (such as primates)

compared to other mammals such as mice as taught by *Simerly et al*, that EM stem cells of mouse and human differ in various aspects, and remain to be determined whether the protocol for differentiating mouse cells are transferable for human EM cells (Citation of *Draper et al*). Particularly, some of the post-filing art have taught that that porcine embryos can be cultured in a defined medium *only* to the blastocyst stage (*Niemann et al*). Regarding selective *in vitro* lineage differentiation in mice and humans, the best results to date is obtaining a *clumps of cells* bearing appropriate surface markers, no single organ has been induced (*Draper et al*). To this end, the cited numerous teachings directly contradict the assertions made in the Declaration. The specification fails to teach what is unknown in the art, and how to overcome the art-known hurdles, thus, it would have required undue experimentation for the skilled artisan intending to practice the instant invention as it is broadly claimed.

D. Applicants then argue that mammalian organs can be induced in vitro using the same methods that are described in the specification for Xenopus without undue experimentation, that method described in the specification are new, thus the success or failure of the cited previously described methods is not relevant to the patentability of the present invention, that the described method should be successful in mammals as well as lower vertebrate, and that the Examiner has not presented any evidence to cast doubt on applicants assertion to this effect. (Response, page 4, paragraphs 4 & 5).

In response, the Xenopus embryo has long served as a major model for the study of *embryonic development* especially the earliest embryonic patterning events because of its numerous advantages, including external development, large size,

identifiable blastomeres, and its ability to withstand extensive surgical intervention and culture *in vitro*. These advantages are acknowledged in the background section of the specification (page 1, 3rd paragraph). On the other hand, these very reasons indicate that it is very difficult to achieve such in the embryos of other vertebrate species. The specification only teaches the method of inducing and culturing xenopus embryo, one species of a large genus. It is noted that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." It is noteworthy that one of applicants' own publication illustrates the unpredictable nature of *in vitro* induced organ formation in subgenus amphibians, wherein *Ariizumi et al* (Int. J Dev Biol 1996;40:715-8) teach that using the same protocol, a beating heart could be induced from newt

ectoderm but not Xenopus ectoderm (both are amphibians), and concluded "THE INDUCTION PROPERTIES OF ACTIVIN ON NEWT ECTODERM ARE DIFFERENT FROM THOSE ON XENOPUS ECTODEM" (right column, page 716, emphasis added). In view of such, the invention does not appear to be fully enabled.

Further, applicants are reminded that all of the following cited references are post-filing art, *Niemann et al, Watt et al, Donovan and Gearhart, Simerly et al, Draper et al*, all illustrated the undeveloped state of the art in *ex vivo* organ development. These citations provide sufficient evidence to conclude that contrary to the assertions of the Declaration, the specification fails to provide an enabling disclosure commensurate with the scope of the claims. M.P.E.P. states, "IF INDIVIDUALS OF SKILL IN THE ART STATE THAT A PARTICULAR INVENTION IS NOT POSSIBLE YEARS AFTER THE FILING DATE, THAT WOULD BE EVIDENCE THAT THE DISCLOSED INVENTION WAS NOT POSSIBLE AT THE TIME OF FILING AND SHOULD BE CONSIDERED. IN *IN RE WRIGHT*, 999 F.2D 1557, 1562, 27 USPQ2D 1510, 1513-14 (FED. CIR. 1993) AN ARTICLE PUBLISHED 5 YEARS AFTER THE FILING DATE OF THE APPLICATION ADEQUATELY SUPPORTED THE EXAMINER'S POSITION THAT THE PHYSIOLOGICAL ACTIVITY OF CERTAIN VIRUSES WAS SUFFICIENTLY UNPREDICTABLE SO THAT A PERSON SKILLED IN THE ART WOULD NOT HAVE BELIEVED THAT THE SUCCESS WITH ONE VIRUS AND ONE ANIMAL COULD BE EXTRAPOLATED SUCCESSFULLY TO ALL VIRUSES WITH ALL LIVING ORGANISMS. CLAIMS NOT DIRECTED TO THE SPECIFIC VIRUS AND THE SPECIFIC ANIMAL WERE HELD NONENABLED". (MPEP 2164.05a). In view of above consideration, the Office has presented sufficient evidence to cast doubt on applicants' assertion to this effect.

E. With respect to transplantation of the cultured organ, applicants argue that the invention is not specifically directed to fetal transplants, and that fetal surgery has been

carried out on a fairly routine basis for a number of years, thus no more than routine experimentation is required to overcome the problems indicated by the Examiner (Response, 2nd paragraph, page 5).

In response, as indicated above, the xenopus embryo is known for withstanding extensive surgical intervention, but not that of the mammals. As to the organ transplantation in fetuses, a quick search of PubMed database would find no hit on this topic, thus, there is no evidence of record supporting the counsel's assertion that fetal surgery is routine at the time the application was filed. Applicants are reminded that the claims require organ transplantation in fetuses, not just any surgical procedure. As to the matured organ transplantation, the specification fails to teach the condition and feasibility of inducing, culturing, and maintaining an organ *ex vivo* from a blastula embryo to the stage of juvenile and adult, whether for a xenopus or for mammals, thus, the pre-requisition of the organ transplantation for children and adults is lacking. In view of these considerations, the claims do not appear to be enabled in the absence of evidence to the contrary.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for inducing a functional organ of any vertebrates *in vitro*, and transplanting such to a vertebrate recipient of any developmental stage, and obtaining a functional organ and a viable fetus, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *ex vivo* organ induction, maintenance, and transplantation for the entire vertebrate genus, it would

have required extensive undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the rejection, Applicants request suggestion from the Examiner, thus it is noted that amending the last phrase of claim 25 to recite, "an organ that functions *in vivo* is obtained" would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The prior rejection of claims 25-27 under 35 U.S.C. 102(a) as being anticipated by *Ninomiya et al* (Develop Growth Differ 1999;41:391-400) is withdrawn in view of the submission of English translation of the foreign priority document.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

Q. Janice Li
Patent Examiner
Art Unit 1632

JANICE LI
PATENT EXAMINER

QL
February 9, 2004